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Post-intestine transplant graft-versus-host disease: Associated with inclusion of a liver graft and with a high mortality risk

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Abbreviations:

ANOVA	Analysis of variance
IBM	International Business Machines
IT	Intestine transplant
GVHD	Graft-versus-host disease
HSC	Hematopoietic stem cell
MELD	Model for end-stage liver disease score
MMVT	Modified multivisceral transplant
MVT	Multivisceral transplant

rATG	Rabbit antithymocyte globulin
SPSS	Statistical package for the social sciences

Abstract

Introduction

This study reports the incidence, anatomic location, and outcomes of graft-versus-host disease (GVHD) at a single active intestine transplant center.

Methods

Records were reviewed for all patients receiving an intestine transplant from 2003 to 2015. Pathology reports and pharmacy records were reviewed to establish the diagnosis, location, and therapeutic interventions for GVHD.

Results

A total of 236 intestine transplants were performed during the study period, with 37 patients (16%) developing GVHD. The median time to onset of disease was 83 days, with 89% of affected patients diagnosed in the first year post-transplant. Mortality for affected patients was 54% in the one-year after GVHD diagnosis.

Skin lesions were the most common manifestation of GVHD. Other sites of disease included lungs, bone marrow, oral mucosa, large intestine, and brain. The incidence of GVHD was 16% in adult patients, and slightly lower in pediatric recipients (13%). In adults, increasing graft volume (isolated versus multi-organ) and liver inclusion were associated with increasing risk of GVHD, though this was not seen in pediatric patients.

Conclusion

Overall, 16% of intestine transplant recipients developed GVHD. GVHD is associated with high mortality, and disease in the lungs, brain, and bone marrow was universally fatal.

Introduction

Intestine transplant is a potentially life-saving procedure for patients who have experienced intestine failure, unresectable mesenteric tumors, portomesenteric thrombosis, among other intraabdominal pathologies. Although advances have occurred, intestine transplant continuous to be replete with risk of morbidity and mortality. Serious post-transplant complications commonly arise limiting the efficacy of the intestine graft as well as the long-term survival of many transplant recipients.

Graft-versus-host disease (GVHD) is a serious and potentially life-threatening complication arising in intestine, other solid organ, and allogenic hematopoietic stem cell (HSC) transplantation. GVHD occurs when T-cells from the donor tissue are activated by host antigen-presenting cells causing donor lymphocytes to initiate an immune response against recipient tissue. All host tissues are susceptible to attack by activated donor cells but the skin, liver, and gastrointestinal tract are the most common sites of disease.[1] The incidence of GVHD in HSC transplantation is high and has been shown to be 50% in some studies.[2]

In solid organ transplantation, the incidence of GVHD is much lower, but varies greatly by type of organ transplanted. Small intestine transplants, whether as a multivisceral graft or as an isolated intestine graft, have the highest incidence of GVHD in solid organ transplantation with disease being seen in over 20% of small bowel recipients.[3, 4] In contrast, GVHD develops in only 1-2% of liver transplant recipients, and only a few case reports of GVHD after kidney transplantation have been reported.[5-7] Although the incidence of GVHD in solid organ transplantation is low, the development of disease can have catastrophic consequences with over 75% mortality associated with GVHD in liver transplant recipients.[5] Clinical predictors of GVHD are not well identified. The size of the

transplant graft relative to the recipient may have an association simply because of the greater volume of transplanted tissue. Alternatively, immunologically active organs such as the liver, intestine and lung may be more likely to attack host tissue as these organs routinely surveil the body for foreign antigens and have a greater capacity to mount an independent immunologic response.

The present study reports the incidence, anatomic location, and outcomes for GVHD in intestine transplant patients at a single center. Subgroup analysis is performed in an attempt to identify those patients at risk for the development of GVHD in this high-risk population.

Methods

Medical records for all patients receiving an intestine transplant at a single center from 2003 to 2015 were retrospectively reviewed. Patients received an isolated intestine transplant (IT) or an intestine transplant en bloc with other organs as a multivisceral transplant (MVT; liver, stomach, pancreas, small intestine) or modified multivisceral transplant (MMVT; stomach, pancreas, small intestine). A subset of patients also received a donor large intestine as part of a small intestine transplant. All patients receiving an intestine allograft were included regardless of transplant type, large intestine inclusion, or outcome.

Graft-versus-host disease was diagnosed based on clinical indications and histopathologic evidence using biopsies from affected areas (skin, bone marrow, lungs). All patients with an unexplained skin rash in the post-transplant period underwent skin biopsy to determine if the rash represented GVHD. In all cases, the dermatopathologists were able to conclusively determine if the rash represented GVHD, versus some other etiology. Diagnosis of GVHD in the lung and bone marrow also required tissue biopsy. Open biopsy of the lung

in an already compromised patient is a challenging clinical decision, and we only pursued lung biopsy in those patients with a compromised pulmonary status for whom all other etiologies had been excluded. Bone marrow biopsy was more easily obtained, but generally just demonstrated a marrow devoid a cellular components. No liver biopsies were taken to assess for GVHD in patients with a liver exclusive graft, therefore no GVHD of the liver is noted. Additionally, a single case of GVHD in the central nervous system was diagnosed via a computed tomography (CT) scan. The CT scan showed demyelination of the brainstem, periventricular white matter, and cerebellar hemispheres bilaterally which is consistent with GVHD in the CNS. Pharmacy records were reviewed in documented cases to assess therapeutic interventions and to confirm therapy administration for the diagnosis of GVHD. At this center, treatment of GVHD consisted of a steroid taper only, and no other therapy was employed. Cutaneous GVHD was graded (I-IV) according to consensus criteria.[8]

Intestine and multivisceral transplant procedures performed at our center have been previously described.[9-11] Intestine decontamination was never administered to the donor or to the recipient as part of intestine transplant process.[12] When another center was procuring the donor pancreas, the duodenum was stapled prior to use of intestine decontamination to prevent exposure of the isolated intestine graft to the decontamination solution.[13] Similar immunosuppression induction therapy was given to each patient and consisted of 3-5 alternating doses of solumedrol (500, 250, 125mg) and rabbit antithymocyte globulin (rATG, total dose 5-6mg/kg) with a single dose of rituximab (150mg/m^2). Tacrolimus (goal level 10ng/dL (early) and 7-8ng/dL (later)) and low dose steroids were used for immunosuppression maintenance.[14] Second agents such as rapamycin, mycophenolate and azathioprine were almost never used in this patient cohort. Infection prophylaxis with broad-spectrum antibiotics was continued for 48 hours post-operatively in most cases, and up to one week post-transplant in cases with significant intraoperative contamination.

Immunosuppression surveillance using cell counts (e.g. CD3) or commercially available markers (e.g. ImmuKnow) was not routinely performed.

Patients were stratified into groups based on age (adults and pediatric) and transplant type (IT, MMVT, MVT) for data analysis. Post-GVHD survival outcomes were measured from the day of GVHD diagnosis, not from the day of transplant. Subgroup analysis was performed to determine the impact of donor to recipient size ratio, to determine if a size disparity increased the risk of GVHD. The mean of the ratio of donor to recipient height, weight, and BMI of affected and non-affected patient groups was utilized. Data were analyzed using the software Statistical Package for the Social Sciences (IBM SPSS Statistics 24, IBM Corporation, Armonk, New York, USA). The institutional review board at Indiana University School of Medicine reviewed and approved the retrospective analysis of data from the transplant database.

Results

Altogether, 236 intestine transplants were performed on 214 patients, with 21 patients undergoing multiple intestine transplant procedures. The median age of transplant recipients was 42 years, with 184 adult patients (>18 years) and 52 pediatric patients (≤18 years). Intestine failure was the primary indication for transplantation in the majority of cases (63%). Portomesenteric thrombosis and non-resectable tumors were the other conditions most commonly necessitating intestine transplant. The majority of patients (62%) received a MVT, while 26% received an IT, and 12% a MMVT. No pediatric patient received a MMVT. Donors had a median age of 18 years, and trauma was the primary cause of death. **[Table 1]**

The rate of GHVD in this cohort of patients was 16%. The incidence of GVHD in MVT was significantly higher (20%) than that seen in MMVT (14%) and IT (7%) (p=0.05). In adult patients, a similar pattern was observed with 22% of MVT, 14% of MMVT, and only 4% of IT patients developing GVHD (p=0.02). In the pediatric population, the overall

incidence was slightly lower (13%) with only a slight difference in the rate between MVT and IT recipients (15% vs. 11%). **[Table 2]** Overall, the median time post-transplant to the development of GVHD in affected patients was 83 days (62 days in pediatrics and 90 days in adults), with 57% of patients diagnosed in the first 90-days post-transplant and 89% within the first year. All affected patients were treated with a long steroid taper until the skin lesions disappeared. With a short course of therapy, the skin lesions often returned. However, in all cases, the lesions did eventually disappear, though a taper of many months duration was required.

A total of six different pediatric patients developed seven cases of GVHD, with one patient developing GVHD after each of their two transplants. Most of the pediatric patients were male (72%) and the majority received a MVT graft (72%). All of the affected pediatric patients had cutaneous manifestations of GVHD, and only one child developed extracutaneous disease, which was found in the lung. All but one pediatric patient (86%) developed disease in the first 90 days post-transplant. Only one (17%) child died from the direct effects of GVHD, and two (33%) died within the first year post-diagnosis. **[Table 3]** It is unclear whether other deaths, most commonly resulting from infection and sepsis, were related to GVHD or its treatment (a prolonged course of moderate dose steroids).

GVHD occurred in 29 different adult patients, with one patient having the disease twice after two separate transplant procedures. Among adult GVHD patients, 80% had received an MVT (n=24), 13% MMVT (n=4) and 7% IT (n=2). There was an even gender distribution. The skin was affected in all but one adult patient, while 10 patients developed extracutaneous manifestations of disease in the bone marrow, lung, gastrointestinal tract, or central nervous system. GVHD manifested itself within the first 90 days post-transplant in 50% of affected adult patients. Ninety percent of affected adult patients had evidence of disease within the first year. There were 41% of affected adult patients alive one year after

initial diagnosis of GVHD, but only three adult patients had GVHD as the primary cause of death. The one-year survival (post-diagnosis) of adult patients with GVHD in the bone marrow, lungs and CNS was even lower (25% (2/8)), and none of these patients was alive at 2 years post-diagnosis. **[Table 3]**

This study finds an increasing graft volume being associated with a higher risk of GVHD. Therefore, an analysis was performed to analyze the ratio of donor to recipient height, weight, and BMI. When comparing these ratios in GVHD and non-GVHD groups the ratios ranged from 0.99 to 1.01, and there was no significant difference between the groups. These data provide evidence that donor to recipient size ratio is not predictive of a diagnosis of GVHD. **[Table 4]** Alternatively, all liver inclusive grafts also had higher graft volume. Subgroup analysis of patients that did and did not receive a liver demonstrated a significantly higher rate of liver inclusion in the GVHD group (78% (GVHD) versus 59% (no GVHD), $p=0.02$), strongly suggesting an independent mechanism for involvement of the liver in this process. Immunologic assessment is also included in **Table 4**. Panel reactive antibody (PRA), T-cell and B-cell crossmatch, and any formation of donor specific antibody (DSA) were not associated with increased risk of GVHD. Patients with a lower human leukocyte antigen (HLA) mismatch number had a lower risk of GVHD (4 versus 5, $p=0.06$). Patients who had experienced any graft rejection were at lower risk for GVHD (14% (GVHD) versus 36% (no GVHD), $p<0.01$).

Discussion

This study reports the incidence, location, and outcomes of GVHD in a large patient population undergoing intestine transplantation at a single center. The incidence among this cohort was 16% which is congruent with previously published data that show GVHD to range from 6% to 29%.[3, 15] The median time to GVHD diagnosis was 83 days, with only four

cases being diagnosed after one-year post-transplant. This suggests that some level of graft-recipient tolerance may develop over time, or that those who are affected have a poor immunologic match and die early within their post-transplant course. Among the 35 patients who developed graft versus host disease, two developed the disease twice, once after their original transplant and again after the subsequent transplant. This suggests that there may be a genetic or immunologic factor that predisposes affected patients to develop GVHD.

Similar to previously published data, the incidence of GVHD in this patient population increased as the size of the graft increased (IT to MMVT to MVT).[15-17] This increase has been speculated to be from an increase in the amount of lymphoid tissue transplanted, but a definitive mechanism has yet to be elucidated.[17] In response to this observation, the present study tested the hypothesis that the ratio of donor to recipient size would be greater than 1.00 in patients who develop GVHD. In theory, as donor size increased in relation to recipient size the volume of immunologically active cells transplanted would be proportionally larger, perhaps leading to an increase in the incidence of GVHD. This hypothesis was not supported by the data as the ratios of height, weight and BMI in all the groups tested varied little from 1.00. Thus, the ratio of donor to recipient height, weight, and BMI does not appear to be an important risk factor for the prediction of GVHD development. A more promising finding was that liver inclusion was associate with higher risk of GVHD ($p=0.02$). The liver is known to be very immunologically active and may mediate this process in these patients. However, GVHD in liver transplant only patients is quite rare, providing evidence against this idea. Further work is needed to identify reliable predictors for the development of GVHD. Also, additional research is required to elucidate the underlying cause of the increase in GVHD incidence among MVT recipients when compared to IT recipients, especially if the liver is involved.

Other variables not analyzed in this paper that may influence the development of GVHD include splenectomy and the use of rATG. Splenectomy has been associated with the development of GVHD in HSC transplantation, but in intestine transplantation, results from previously published reports are conflicting.[15, 16, 18] Previous reports have shown that the use of rATG decreases the incidence of GVHD in reduced-intensity stem cell transplantation and may have a similar effect in intestine transplantation.[19, 20] rATG may have similar effects on incidence of GVHD in this cohort, but this is impossible to determine without a comparison group as all patients in this cohort did receive rATG.

As previously noted from existing publications, GVHD in solid-organ transplantation is associated with high post-transplant mortality.[5] A similar trend is observed in intestine transplantation, with 77% of patients dying within the follow-up period, with a median time to death of 12.6 months post diagnosis of GVHD.[16] High mortality was also observed in the patient population from the present study, with 54% of patients dying during the first year after diagnosis (19 of 35). While only four of these deaths were directly attributed to GVHD, increased immunosuppression to treat GVHD may have contributed to others. Besides the 4 patients who died from GVHD, there were 10 more who died of infection (sepsis) within 90 days of receiving a steroid taper as treatment for GVHD. The argument can be made, then, that 14 of 19 deaths were related to GVHD (74%), though this cannot be definitively proven. The high mortality among this vulnerable population highlights the need for novel treatment options for GVHD.

Currently, there is no consensus on the best therapy to reverse GVHD, and treatment options are lacking in effectiveness. Described treatment options consist of increasing immunosuppression, whether through a steroid taper, anti-lymphocytic drugs, anti-interleukin-2 antibodies, or other biologic therapies.[21, 22] Cell based treatments are now being studied, but none have gained widespread use. Mesenchymal stem cell therapy has

been described as GVHD prophylaxis, and was effective in a small patient cohort.[23] Extracorporeal photophoresis has also been reported as therapy for GVHD, but this was reported to be ineffective.[3] Novel therapies targeting Jak-1/Jak-2 such as ruxolitinib have shown promise in treating acute and steroid-resistant GVHD, potentially offering another treatment option for patients who suffer from this complication.[24]

In conclusion, graft-versus-host disease is a serious and potentially life-threatening complication occurring after HSC and solid-organ transplantation. Currently, there are few effective treatment options, and further work is required to develop to effect therapies. Results from this study suggest that GVHD in the intestine transplant population is more likely to be seen in patients receiving a liver graft, those with a worse HLA match and patients who have not experienced any rejection. Donor-recipient size discordance does not appear to predict GVHD in this population. GVHD is associated with high mortality in a patient population known to have poor long-term survival.

References

1. Ratanatharathorn, V., et al., *Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation.* Blood, 1998. **92**(7): p. 2303-14.
2. Jacobsohn, D.A. and G.B. Vogelsang, *Acute graft versus host disease.* Orphanet J Rare Dis, 2007. **2**: p. 35.
3. Feito-Rodriguez, M., et al., *Cutaneous graft versus host disease in pediatric multivisceral transplantation.* Pediatr Dermatol, 2013. **30**(3): p. 335-41.
4. Shin, C.R., et al., *Incidence of acute and chronic graft-versus-host disease and donor T-cell chimerism after small bowel or combined organ transplantation.* J Pediatr Surg, 2011. **46**(9): p. 1732-8.
5. Smith, D.M., et al., *Liver transplant-associated graft-versus-host disease.* Transplantation, 2003. **75**(1): p. 118-26.
6. Taylor, A.L., et al., *Monitoring systemic donor lymphocyte macrochimerism to aid the diagnosis of graft-versus-host disease after liver transplantation.* Transplantation, 2004. **77**(3): p. 441-6.
7. Guo, Y., et al., *Graft-versus-host-disease after kidney transplantation: A case report and literature review.* Medicine (Baltimore), 2017. **96**(26): p. e7333.
8. Przepiorka, D., et al., *1994 Consensus Conference on Acute GVHD Grading.* Bone Marrow Transplant, 1995. **15**(6): p. 825-8.
9. Vianna, R.M., et al., *Multivisceral transplantation for diffuse portomesenteric thrombosis.* Ann Surg, 2012. **255**(6): p. 1144-50.

10. Vianna, R., et al., *Intestinal and multivisceral transplantation at Indiana University: 6 years' experience with 100 cases.* Clin Transpl, 2009: p. 219-28.
11. Vianna, R., et al., *Safe inclusion of the entire pancreas as a component of the multivisceral graft.* Transplantation, 2008. **86**(1): p. 114-6.
12. Clouse, J.W., et al., *Posttransplant complications in adult recipients of intestine grafts without bowel decontamination.* J Surg Res, 2018. **225**: p. 125-130.
13. Fridell, J.A., et al., *Outcomes of pancreas allografts procured simultaneously with an isolated intestine allograft: single-center and national data.* Transplantation, 2012. **94**(1): p. 84-8.
14. Vianna, R.M., et al., *Induction immunosuppression with thymoglobulin and rituximab in intestinal and multivisceral transplantation.* Transplantation, 2008. **85**(9): p. 1290-3.
15. Mazariegos, G.V., et al., *Graft versus host disease in intestinal transplantation.* Am J Transplant, 2004. **4**(9): p. 1459-65.
16. Wu, G., et al., *Graft-versus-host disease after intestinal and multivisceral transplantation.* Transplantation, 2011. **91**(2): p. 219-24.
17. Cromvik, J., et al., *Graft-versus-host Disease After Intestinal or Multivisceral Transplantation: A Scandinavian Single-center Experience.* Transplant Proc, 2016. **48**(1): p. 185-90.
18. Michallet, M., et al., *Role of splenectomy in incidence and severity of acute graft-versus-host disease: a multicenter study of 157 patients.* Bone Marrow Transplant, 1991. **8**(1): p. 13-7.
19. Bond, G.J., et al., *Evolutionary experience with immunosuppression in pediatric intestinal transplantation.* J Pediatr Surg, 2005. **40**(1): p. 274-9; discussion 279-80.
20. Nakai, K., et al., *Antithymocyte globulin affects the occurrence of acute and chronic graft-versus-host disease after a reduced-intensity conditioning regimen by modulating mixed chimerism induction and immune reconstitution.* Transplantation, 2003. **75**(12): p. 2135-43.
21. Mawad, R., A. Hsieh, and L. Damon, *Graft-versus-host disease presenting with pancytopenia after en bloc multiorgan transplantation: case report and literature review.* Transplant Proc, 2009. **41**(10): p. 4431-3.
22. Green, T. and J. Hind, *Graft-versus-host disease in paediatric solid organ transplantation: A review of the literature.* Pediatr Transplant, 2016. **20**(5): p. 607-18.
23. Dogan, S.M., et al., *Mesenchymal stem cell therapy in patients with small bowel transplantation: single center experience.* World J Gastroenterol, 2014. **20**(25): p. 8215-20.
24. Zeiser, R., et al., *Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey.* Leukemia, 2015. **29**(10): p. 2062-8.

Table 1. Demographics for 236 consecutive intestine transplant patients.

	Overall	Adult	Pediatric
Number	236 (100%)	184 (78%)	52 (22%)
Recipients			
Age (years, median, range)	42	50 (19 - 67)	1.6 (0.3 - 18)
Gender: male	50%	47%	60%
Race: White	83%	89%	65%
Disease			
Portomesenteric thrombosis	24%	30%	6%
Tumor	13%	16%	2%
Intestine failure / Other	63%	54%	92%
Transplant type			
Intestine only	26%	24%	35%
Modified multivisceral	12%	15%	0%
Full multivisceral	62%	61%	65%
Donors			
Age (year, median, range)	18	19 (4 - 50)	1.5 (0.1 - 22)
Gender: male	56%	59%	46%
Race: White	71%	75%	57%
Cause of death			
Stroke	12%	13%	12%
Trauma	59%	62%	46%
Anoxic brain injury	29%	25%	42%

Table 2. Incidence of GVHD by age and transplant type

	No. of Patients	Overall	Isolated Intestine	Modified Multivisceral	Multivisceral	p-value
Combined	236	16%	7%	14%	20%	0.05
Pediatric	52	13%	11%	-	15%	0.72
Adult	184	16%	4%	14%	22%	0.02

Table 3. Characteristics of 37 patients who developed GVHD.

Patient	Gender	Transplant Type	Skin Grade	Other Location	Days to Diagnosis Post-transplant	Outcome	Cause of Death
Pediatric							
1	Female	MVT	II	-	61	Died, day 123	Pseudoostruction, adenovirus
2	Male	MVT	Unknown	Lung	67	Died, day 237	GVHD Lung
3	Male	Intestine only	II	-	55	Alive, day 2499	-
4	Male	Intestine only	II	-	85	Died, day 594	Liver failure, chronic rejection
5	Male	MVT	II	-	35	Died, day 475	Liver failure, chronic rejection
6	Female	MVT	II	-	800	Alive, day 631	-
7	Male	MVT	II	-	62	Alive, day 358	-
Adult							
8	Male	MMVT	II	-	28	Died, day 379	CMV disease
9	Male	MVT	II	-	45	Died, day 93	Fungal sepsis
10	Male	MVT	II	-	495	Died, day 171	Myocardial infarction
11	Male	MVT	II	Bone Marrow	122	Died, day 134	GVHD of bone marrow
12	Female	MVT	II	-	27	Died, day 17	Sepsis, enterobacter
13	Male	MVT	II	-	29	Died, day 7	Sepsis; fungal, VRE
14	Male	MVT	II	-	108	Died, day 312	Sepsis
15	Male	MMVT	II	Lung	34	Died, day 225	Sepsis; pneumonia
16	Female	MVT	II	Oral Mucosa	217	Died, day 369	Renal Failure
17	Female	MVT	II	-	22	Died, day 1580	Chronic aspiration, sepsis
18	Female	MVT	II	-	27	Died, day 233	GVHD
19	Female	MVT	II	Bone Marrow	350	Died, day 613	Acute myeloid leukemia
20	Male	MVT	III	Colon	128	Died, day 472	HCV Treatment; sepsis
21	Male	MVT	-	Bone Marrow	32	Died, day 263	Sepsis; malnutrition
22	Male	MVT	II	-	87	Alive, day 2031	-
23	Male	MVT	II	Lung	125	Died, day 401	Pancytopenia, sepsis
24	Male	MVT	Unknown	-	121	Alive, day 1668	-
25	Female	MVT	II	-	59	Died, day 1369	Sarcoma in liver
26	Female	MMVT	II	Bone Marrow	92	Died, day 29	Chronic fungal sepsis
27	Female	Intestine Only	Unknown	-	419	Died, day 99	HSV infection
28	Male	MVT	III-IV	CNS, Oral Mucosa	32	Died, day 216	Hemorrhagic stroke
29	Male	MVT	II	-	41	Alive, day 1097	-
30	Female	MVT	II	-	167	Died, day 313	Sepsis
31	Female	MVT	II	-	177	Died, day 288	Respiratory failure; sepsis
32	Male	MVT	II	Bone Marrow	83	Died, day 247	GVHD of bone marrow
33	Female	MVT	II	-	30	Died, day 214	Respiratory failure; sepsis
34	Female	MVT	II	-	24	Alive, day 290	-
35	Female	MVT	Unknown	-	116	Died, day 156	Acute graft thrombosis
36	Female	MMVT	Unknown	-	267	Died, day 394	Unknown; alcoholism
37	Female	Intestine Only	II	-	392	Alive, day 1476	-

Table 4. Ratio of donor to recipient (means) based on height, weight, and BMI. Analysis by immunologic status.

	No GVHD	GVHD	p-value
	N=199	N=37	
Donor to recipient size			
Height Ratio	0.99	1.00	0.73
Weight Ratio	1.00	1.01	0.92
BMI Ratio	1.00	1.00	0.93
Presence of liver			
Liver inclusive	59%	78%	0.02
No liver	41%	22%	
Panel reactive antibody			
Class I (mean, median)	0, 14	0, 6	0.14
Class II (mean, median)	0, 11	0, 7	0.44
Crossmatch (flow)			
T-cell positive	16%	8%	0.23
B-cell positive	17%	11%	0.41
Human leukocyte antigen			
Mismatch number (mean, median)	5,5	4,4	0.06
Any donor specific antibody	19%	11%	0.25
Post-transplant rejection			
Any	36%	14%	<0.01
None	64%	86%	